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Prostaglandin E1 before Elective Caesarean Section to Reduce Transient Tachypnea of the Newborn (TTN): A Randomized Control Trial

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ABSTRACT

Aim of the study: this study aimed to determine the role of prostaglandin E1 on the reduction of the neonatal respiratory morbidity specially (TTN). **Study Design:** this is a parallel, randomized placebo controlled trial, comparing the use of Misoprostol (Prostaglandin E_1) use in the form of Misoprostol E_1 vaginal tablets with nonmedicated similar vaginal tablet (placebo) to decrease the neonatal respiratory distress specially (TTN). **Results:** this study included 300 cases with gestational age range between 38 weeks to less than 39 weeks the included cases were classified into 2 groups: study group included 150 case were given PG E1 control group included 150 case were given placebo. **Conclusion**: we found one positive cases for TTN in study group, and 3 positive cases for TTN in the control group results we got were insignificant. So, we suggested taking more large sample in the future studies.

Keywords: prostaglandins cesarean section respiratory morbidity transient tachypnea of newborn.

INTRODUCTION

Neonatal respiratory distress occur more in preterm newborn than term newborn and whether born vaginally or through caesarean section, but in a higher percentage after elective caesarean than after normal vaginal delivery **(1).** Transient tachypnea of the newborn (TTN) occurred due to delayed resorption of pulmonary fluid, as a result of defective catecholamine surge **(2).** Catecholamines can stimulate pulmonary fluid reabsorption through acting upon beta-adrenergic receptors in foetal lung which present more late in gestation, and thus enable the secretion of surfactant **(3).** This surge of catecholamines can be provoked through prostaglandins given before caesarean section to pregnant females (4) as those who are born vaginally are found to be adapted metabolically through a higher catecholamine level at birth **(4).** So, prostaglandins may be given about one hour before an elective caesarean section after excluding the presence of contraindication to their use to decrease the neonatal respiratory distress **(5).** In a previous similar prospective study of 36 women scheduled for an elective caesarean section beyond 38weeks **(4)** 18 women received intravaginal prostaglanadin E2 tablets and 18 received placebo, there was one neonatal respiratory distress case in the control group which was reported as transient tachypnea of the newborn with similar Apgar score at one and five minutes and no need to mechanical ventilation nor side effects related to treatment in either group, so no difference in respiratory outcome was reported.

PATIENTS AND METHODS

Study Setting

This study was conducted in Ain Shams University Maternity Hospital (ASUMH) and Police Hospital- Nasr City and it started from November 2016 to July 2017.

Trial Design

Parallel, randomized placebo controlled trial, comparing the use of Misoprostol (Prostaglandin E_1) use in the form of Misoprostol E_1 vaginal tablets with non medicated similar vaginal tablet (placebo) to decrease the neonatal respiratory distress specially (TTN).

Eligibility Criteria

- ***Inclusion criteria***
- Age: 18 years or more.
- Term pregnancy (38 - < 39 weeks).
- Pregnant women planned for elective transverse lower segment caesarean section with an indication. A written informed consent signed by the participating women.
- ***Exclusion criteria***
- Women with history of significant cardiac disease, D.M, eclampsia, pre eclampsia, epilepsy, severe asthma, severe allergic condition, vascular disease, renal or hepatic disease.
- Women with contraindication to prostaglandins as Glucoma or known hypersensitivity to prostaglandins or specifically for Misoprostol.
- Psychological problem or mental disease that renders the patient not able to understand the nature, scope, and sequences of the study.
- Pregnancies with known foetal malformation/s or chromosomal aberration.

INTERVENTION

- **Subjects**

The population in this study was consisted of a sample of pregnant women between 38 - < 39 weeks gestation scheduled for elective caesarean

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section, selected according to inclusion and exclusion criteria, we took 300 cases randomly and they were distributed into two groups:

- The first group (Group E) included 150 women and they were treated with Misoprostol (prostaglandin E_1).
- The second one (Group P) was consisted of 150 women and they were given placebo.

Misoprostol (Prostaglandin E1) containing vaginal tablet in the form of Cytotec ® 200 microgram Misoprostol (manufactured by: Pfizer) administered about 60 minutes before scheduled caesarean section. Placebo was given in the form of non Prostaglandin E_1medicated vaginl tab. And it contained only the inactive ingredients (Hydrogenated castor oil, Microcrystalline cellulose, Crospovidone).Patients were synthesized with the help of Laboratories of Ain Shams Faculty of Pharmacy to be administered vaginally for the purpose of research.

OUTCOMES

- **The primary outcome**

Incidence of TTN: there were 3 cases of TTN in the control group and one case in study group [Risk ratio (RR) was 0.50].

- **Secondary outcomes**

Apgar score was reported at one and five minutes with the mean score being nine (8.2) and 9.5 (8.9) respectively for the intervention group. For the control group, the scores were 8.1 at one minute and (8.8) at five minutes.
The need of neonates for mechanical ventilation: none of the neonates required mechanical ventilation.

Percentage of neonates required admission into the intensive care unit: we found one case in the studied group and 2 cases in the control group needed NICU admission.

Fetal mortality in the studied population: there was no death in the studied population.

Conclusion: effect of PG E1 in reducing the incidence of TTN in newborn was insignificant.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

RESULTS

Table 1: demographic characteristics among both groups

Variables		Study (N=150)	Control (N=150)	P
Age (years)	**Mean±SD**	28.4±2.9	28.1±2.7	^0.279
	Range	22.0–35.0	21.0–36.0	
BMI (kg/m^2)	**Mean±SD**	28.4±1.6	28.5±1.8	^0.660
	Range	25.2–32.2	25.1–32.7	
Parity (n, %)	**Primi**	53 (35.3%)	51 (34.0%)	#0.808
	Multi	97 (64.7%)	99 (66.0%)	
Previous CS (n, %)		24 (16.0%)	26 (17.3%)	#0.757

Independent t-test, #Chi square test

There was no significant difference between the studied and control groups regarding **demographic characteristics.**

Table 2: neonatal condition among both groups

Variables		Study(N=150)	Control(N=150)	P
APGAR 1	**Mean±SD**	8.2±0.6	8.1±0.6	^0.156
	Range	6.0–9.0	5.0–9.0	
APGAR 5	**Mean±SD**	8.9±0.6	8.8±0.6	^0.142
	Range	7.0–10.0	6.0–10.0	
NICU (n, %)		1 (0.7%)	2 (1.3%)	#0.624
Mortality		0 (0.0%)	0 (0.0%)	--

^Independent t-test, #Fisher's Exact test

There was no significant difference between the study and the control groups regarding **neonatal condition.**

Table 3: respiratory rate (cycle/minute) among both groups

Measures	Study (N=150)	Control (N=150)	^P
Mean±SD	48.9±4.4	51.7±5.6	**<0.001***
Range	40.0–63.0	40.0–86.0	
Value of study over control			
Items	**Mean±SE**	**95% CI**	
Respiratory rate reduction	2.8±0.6	1.7–3.9	

^Independent t-test, *Significant, CI**:** confidence interval

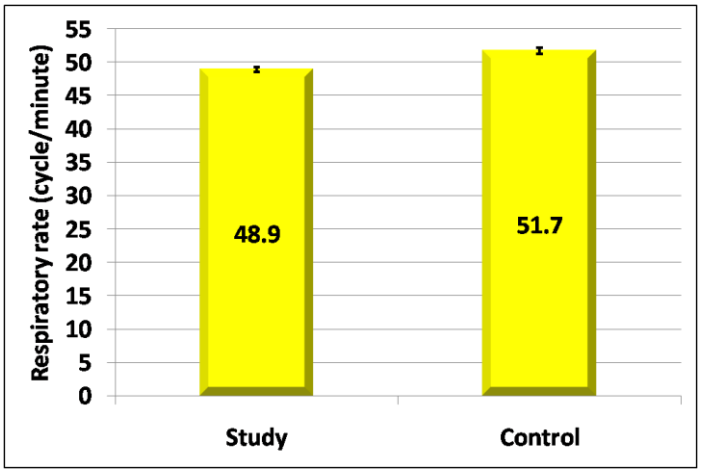

Figure 1: respiratory rate among the studied groups.

Table 3 and figure 1 showed that **respiratory rate** was significantly lower among the studied group than among the control group.

Table 4: respiratory condition among the studied groups

Findings	Study (N=150)	Control (N=150)	#P	RR (95% CI)
Tachypnea RR>60.0	1 (0.7%)	3 (2.0%)	0.622	0.50 (0.03–3.19)
Retraction	0 (0.0%)	1 (0.7%)	1.000	--
TTN	1 (0.7%)	3 (2.0%)	0.622	0.50 (0.03–3.19)

#Fisher's Exact test, RR: Relative risk, CI**:** confidence interval

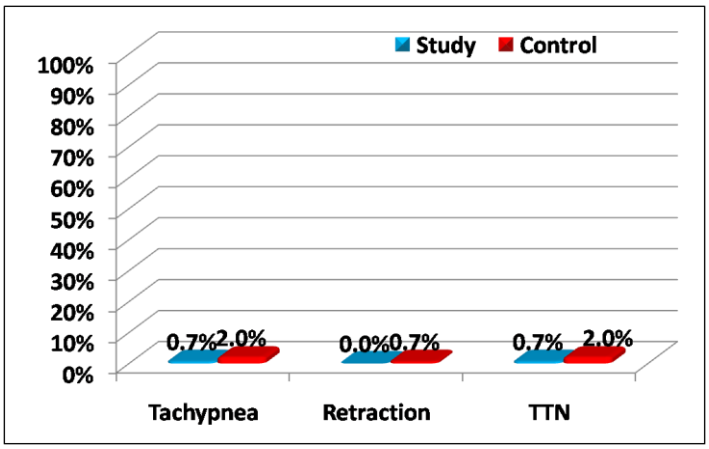

Figure 2: respiratory conditionl among the studied groups.

Table 4 and figure 2 showed that there was no significant difference between both groups as regard tachypnea, retractions and TTN. There was no complication to PE occurred in our current study as uterine hyperstimulation, uterine rupture or meconuim staining of liquor.

DISCUSSION

Respiratory distress (RD) can occur in all newborns irrespective of gestational age or mode of delivery. It accounts for about 30% of neonatal deaths [6] and can occur at birth or several hours after delivery [3]. Infants born by elective caesarean section (CS) delivery at term are at increased risk for developing respiratory disorders, compared with babies delivered per vagina or by emergency CS [7],the relative risk increased with decreasing gestational age. The prevalence of deliveries by CS has been steadily increased worldwide over the last few years[8].
TTN occurred in about five or six per 1,000 births [9].
TTN results from delayed reabsorption and clearance of alveolar fluid showed that post-delivery prostaglandin release distended lymphatic vessels, which removed lung fluid as pulmonary circulation increased with the initial fetal breath. Cesarean delivery without labor bypasses this process and it was therefore a risk factor for TTN Surfactant deficiency may play a role in TTN[10].

Prostaglandins can stimulate surfactant secretion and reduce lung fluid by provoking a catecholamine surge, but it is unclear how early they have to be administered before CS in order to produce this effect. A randomized controlled trial found an increase in catecholamine levels in fetal blood in the intervention group compared with the placebo group, when prostaglandin E2 was administered as intravaginal gel 60 minutes before CS [4].

Decades ago, it was suggested that poor respiratory outcomes in infants delivered by elective CS was explained by delayed absorption of liquid in the lung due to lack of a catecholamine surge[2].

The concentration of beta-adrenergic receptors in the lung tissue was known to increase late in gestation, which might render the lungs more responsive to the effects of epinephrine [11]. Catecholamines thus promote surfactant secretion [3] and stimulate reabsorption of lung fluid from the fetal lung [11]. This catecholamine surge can be stimulated by administering prostaglandins to the pregnant woman before delivery[4].

Prostaglandins can stimulate surfactant secretion and reduce lung fluid by provoking a catecholamine surge [4]. There were no previous similar studies done in this trial except one done using PE 2 by[12] there were 36 women in the one included study, 18 received intravaginal prostaglandin E 2 gel and 18 received placebo. One neonate in the control group developed respiratory distress, it was reported as transient tachypnoea of the newborn by the authors; none of the neonates required mechanical ventilation and the Apgar scores at one and five minutes where similar both groups with no admissions. Neonatal intensive care occurred, two neonates in the control group were admitted into special care. No further information was provided on the reasons for these admissions.

Outcomes indicated respiratory status did not differ significantly between intervention and the control group and there were no treatment-related side effects. Noradrenaline concentrations were significantly higher in the cord blood samples of the intervention group.

In the current study, a randomised placebo-controlled study that was carried out in Ain Shams University Maternity Hospital (ASUMH) and Police Hospital, Nasr City. There were 300 patients in the intervention and 150 in the control group. Participants were pregnant women at term with an indication for elective caesarean section (ECS). Excluded from this study were: pregnancies with known fetal malformations or chromosomal aberration, presence of absolute contraindications for use of prostaglandin E1 vaginal tablets , for example, history of adverse reactions to prostaglandin preparations, CS before 38 week's gestation and failure to obtain informed consent. This study compared 2 mg of prostaglandin E1 tabletes with placebo (K-Y jelly) when administered as intravaginal tablets 60 minutes prior to ECS. This study aimed to assess the reduction of TTN in the prostaglandin E1 group than the placebo group. Other assessed outcomes included Apgar score at one and five minutes, neonatal respiratory distress, admission into a neonatal special care, arterial and venous pH measurements.

Authors used non-parametric (Mann-Whitney-Wilcoxon test and Fisher's exact test) to compare both groups. P values were reported we found 4 positive cases in the control group VS 1 positive case in the studies group and it looks like insignificant results actually its recommended to take a much bigger sample next trial.

In our study, respiratory condition was non-significantly better among the studied group than among the control group. But, respiratory rate was significantly lower among the studied group than among the lcontrol group.

CONCLUSION

The effect of PG E1 in reducing the incidence of TTN in newborn was insignificant.

RECOMMENDATIONS

It's not recommended to use PG E1 before C.S for reducing incidence of TTN as it came insignificant.

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